ARPHA Preprints

PENSOFT

PREPRINT

Author-formatted, not peer-reviewed document posted on 19/11/2021

DOI: https://doi.org/10.3897/arphapreprints.e78186

Possible effect of alkalization therapy on SARS-CoV-2 virus lifecycle

Khaled Elsadani

ARPHA Preprints *Author-formatted, not peer-reviewed document posted on 19/11/2021*. DOI: https://doi.org/10.3897/arphapreprints.e78186

Possible effect of alkalization therapy on SARS-CoV-2 virus lifecycle

Khaled Elsadani ‡

‡ Pediatrician, did Molecular Biology studies., Mansoura, Egypt

Corresponding author: Khaled Elsadani (khaledalsaadani@hotmail.com)

Reviewable v 1

Abstract

This proposal tries to drive attention to the observation that pH variation plays a fundamental role in the functional mechanism of SARS-CoV-2 virus proteases. Depending on this role, testing the effect of alkalization therapy on the SARS-CoV-2 patients could be reasonable.

Keywords

SARS CoV2, SARS-CoV-2 Treatment, SARS-CoV-2 Pandemic control.

Overview and background

The already FDA-approved protease inhibitors for HIV-1, and HCV (Anderson et al. 2009) achieved a significant positive clinical outcome, and so proved that viral proteases are potential targets for the antiviral drug development.

SARS-CoV-2 has its own two proteases; 3CLpro, also known as Mpro, which is the main protease, and the PLpro protease (Zhu et al. 2021).

SARS-CoV-2 3CLpro is a cysteine protease with the catalytic residues cysteine and histidine at its active site (Ullrich and Nitsche 2020).

SARS-CoV PLpro is a papain-like protease which also acts by the cysteine protease catalytic cycle, where histidine functions as a general acid-base (Báez-Santos et al. 2015).

Histidine residue plays a fundamental role in the functional mechanism of such proteases, and this role depends on the histidine residue acting as a general base accepting proton at the beginning of the catalytic cycle, while acting as general acid giving a proton at end of the cycle (Berg et al. 2002) Fig. 1.

This chemical shift is dependent on the pH: that histidine is found to be biprotonated only in acidic pH. However, it becomes deprotonated in alkaline pH (Li and Hong 2011).

At pH 7.0, the nonprotonated form of the histidine residue is dominant. At pH 5.0, the imidazole group is protonated and prefers a hydrophilic environment (Rotzschke et al. 2002).

Objectives

The hypothesis is that the catalytic cycle of SARS-CoV-2 proteases could be broken in case that histidine residues at the proteases active sites are deprived of the suitable pH.

Impact

The idea of this trial is to use alkalizing medications to raise extracellular pH, and subsequently the intracellular pH to a level and period of time that might be effective to deprive histidine residues from the acidic pH required for its protonation, and this may result in stopping its activity, and inhibits the virus proteases.

Even if this trial is successful to interfere with the viral life cycle, this likely applies only in simple forms of the disease. This success could be effective in controlling the pandemic state, that the required therapeutic agents are inexpensive and would be easily supplied all over the world.

Implementation

There are well known medications safely used in current medical practice to affect the human body pH.

Testing the efficacy of repurposing these agents to treat SARS-CoV-2 patients is suggested. Alkalization therapy could be applied in a double blind randomized clinical trial to assess if it could affect the course of the disease.

Of course it's suitable that regimens would be different according to severity of the disease, and condition of the patient. So it's suggested to design two separate experiments; one includes severely ill patients, and another for patients with simple forms of the disease.

References

- Anderson J, Schiffer C, Lee S, Swanstrom R (2009) Viral Protease Inhibitors. Antiviral Strategies85-110. https://doi.org/10.1007/978-3-540-79086-0_4

- Báez-Santos Y, St. John S, Mesecar A (2015) The SARS-coronavirus papain-like protease: Structure, function and inhibition by designed antiviral compounds. Antiviral Research 115: 21-38. https://doi.org/10.1016/j.antiviral.2014.12.015
- Berg JM, Tymoczko JL, Stryer L (2002) Section 9.1. Proteases: facilitating a difficult reaction. Biochemistry. 5th Edition. W.H. Freeman, New York. URL: https://www.ncbi.nlm.nih.gov/books/NBK22526/. [ISBN 978-0-7167-3051-4].
- Li S, Hong M (2011) Protonation, Tautomerization, and Rotameric Structure of Histidine: A Comprehensive Study by Magic-Angle-Spinning Solid-State NMR. Journal of the American Chemical Society 133 (5): 1534-1544. https://doi.org/10.1021/ja108943n
- Rotzschke O, Lau JM, Hofstatter M, Falk K, Strominger JL (2002) A pH-sensitive histidine residue as control element for ligand release from HLA-DR molecules. Proceedings of the National Academy of Sciences 99 (26): 16946-16950. https://doi.org/10.1073/pnas.212643999
- Ullrich S, Nitsche C (2020) The SARS-CoV-2 main protease as drug target. Bioorganic & Medicinal Chemistry Letters 30 (17). https://doi.org/10.1016/j.bmcl.2020.127377
- Zhu W, Shyr Z, Lo D, Zheng W (2021) Viral Proteases as Targets for Coronavirus Disease 2019 Drug Development. Journal of Pharmacology and Experimental Therapeutics 378 (2): 166-172. https://doi.org/10.1124/jpet.121.000688

ARPHA Preprints *Author-formatted, not peer-reviewed document posted on 19/11/2021*. DOI: https://doi.org/10.3897/arphapreprints.e78186

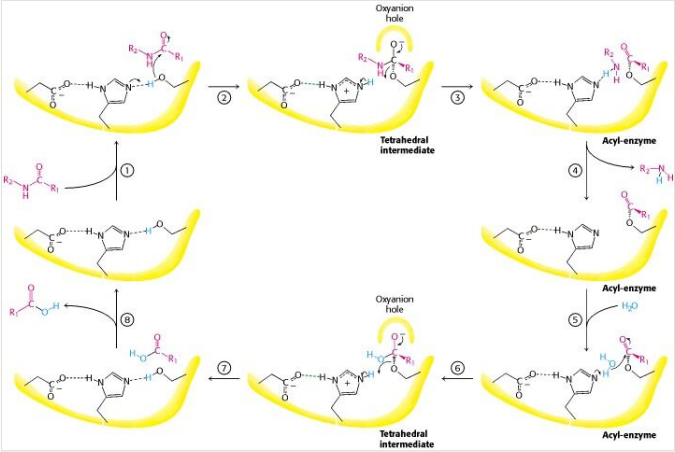

Figure 1.

Functional mechanism of Chymotrypsin like proteases (Berg et al. 2002).